

## **Protocol for a preliminary evaluation of *ante-mortem* TSE tests for ruminants<sup>1</sup>**

### **Scientific Opinion of the Panel on Biological Hazards**

**(Question No EFSA-Q-2007-054)**

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#### **SUMMARY**

Annex X to Regulation (EC) No 999/2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies lists the approved rapid tests which may be used within the framework of the EU monitoring programmes. The European Commission (EC) requested the European Food Safety Authority (EFSA) to take over the mandate of the former Scientific Steering Committee (SSC) for the scientific evaluation of rapid TSE tests. At present and following previous calls for expression of interest, 12 rapid BSE test kits for BSE testing in cattle and 8 rapid tests for TSE testing in small ruminants (sheep and goats) are approved by the EC for the routine *post-mortem* testing in the whole European Union. No test for *ante-mortem* TSE testing in ruminants has currently been approved.

For the second half of 2007, the EC plans to launch a new open call for expression of interest for companies to submit tests for evaluation and potential approval to be used within the framework of EU wide TSE monitoring. This call is intended to include tests for TSE detection in ruminants and to cover *post-mortem* and *ante-mortem* testing. Evaluation of tests is based on protocols developed by experts and includes an assessment of the application dossier, a laboratory trial and a field trial. In preparation of this new call for expression of interest, EFSA was asked by the EC to revise its existing protocols for the evaluation of TSE tests taking into account experience gained in the past evaluation rounds. Two protocols were revised and published (EFSA 2007 a and b) which cover the evaluation of *post-mortem* tests for cattle and sheep and goats.

This current opinion includes a revised protocol describing the preliminary evaluation of *ante-mortem* tests to detect TSE in ruminants. It outlines a general proof of principle and provides

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preliminary guidance to test developers on necessary investigations that should precede any formal evaluation. Defined performance criteria should ensure that such test could be of sufficient interest for their potential consideration as tool that could be integrated in the global strategy for TSE monitoring. Considering the current stage in knowledge and potential scarcity of appropriate biological samples to conduct the pre-evaluation process, no binding performance requirement is felt appropriate at this stage and a recommendation for further evaluation will be at the discretion of EFSA. Therefore, more details on the tissues and/or fluids to be evaluated can be provided only after details are available on the tests once they have been submitted for evaluation.

**Key words:** BSE, Bovine Spongiform Encephalopathy, TSE, Transmissible Spongiform Encephalopathy, live animal test, evaluation, field trial.

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## **BACKGROUND**

Annex X to Regulation (EC) No 999/2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies lists the approved rapid tests which may be used within the framework of the EU monitoring programmes. According to EU legislation samples of CNS from cattle and small ruminants have to be tested using one of the approved<sup>2</sup> “rapid TSE tests”. Only *post-mortem* tests have been approved for this purpose so far. Twelve test kits from ten manufacturers are available for testing for BSE in cattle (EC, 2002; SSC, 2003; EFSA 2004a and 2005a) and 8 for TSEs in small ruminants (EFSA, 2005 b and c) after having been evaluated and subsequently approved by the EC. The approval of these rapid *post-mortem* tests was based on SSC and EFSA evaluation protocols (SSC, 2002; EFSA, 2004b and 2007 a and b) and its recommendations on the suitability or otherwise of the evaluated tests for inclusion in the EU programme for TSE monitoring.

In the last EU call for expression of interest (2003) a number of *ante-mortem* tests were submitted for evaluation. This evaluation was based on a protocol provided by EFSA (EFSA, 2004c). From the submitted test, one test was allowed into the full evaluation process, however after the analysis of the results, the test was not recommended for approval (EFSA, 2006).

## **MANDATE**

The EC is planning to launch a new open call for expression of interest for rapid tests for use in the framework of TSE monitoring. This call is intended to cover tests for TSE detection *ante* and *post-mortem* in ruminants. In order to achieve this, and to prepare the necessary documentation, there is a need to update and if needed to revise current evaluation protocols. The revised protocols will be the basis for any future evaluation rounds of rapid *ante*- and *post-mortem* tests.

The EFSA was requested to revise the current protocols for the test evaluation, taking into account experience gained in past evaluation rounds.

These protocols include:

- Scientific Report of the European Food Safety Authority on the Design of a Field Trial Protocol for the Evaluation of BSE Tests for Live Cattle adopted on 1 July 2004 (EFSA, 2004c);
- Scientific Report of the European Food Safety Authority on the Design of a Field Trial Protocol for the Evaluation of New Rapid BSE *post-mortem* Tests adopted on 5 April 2004 (EFSA, 2004b);
- Opinion on a programme for the evaluation of rapid *post-mortem* tests to detect TSE in small ruminants adopted by the Scientific Steering Committee at its meeting of 7-8 November 2002 (SSC, 2002).

## **ACKNOWLEDGMENTS**

The Experts of the working group are acknowledged for their work for this mandate. The Members are: Olivier Andreoletti (Chairman), Jean-Noel Arsac, Thierry Baron, Anne-Gaëlle Biacabe, Martin Groschup, Jim Hope, Peter Lind, Heinz Schimmel, Emmanuel Vanopdenbosch, Danny Matthews (Rapporteur), Angus Wear, Katherine Webster.

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<sup>2</sup> As laid down in Annex 10, chapter C to Regulation 999/2001

## PROTOCOL

### 1. Preamble

This revised protocol describes criteria for the preliminary evaluation of *ante-mortem* tests to detect TSE in ruminants. Defined performance criteria should ensure that such test could be of sufficient interest for their potential consideration as tool that could be integrated in the global strategy for TSE monitoring. This document describes a preliminary approach to evaluation which enables companies to submit a dossier containing sufficient evidence of proof of principle to allow scope for subsequent formal evaluation. Final evaluation will depend on the individual technical specifications of the submitted tests, *i.e.* target analyte, and the availability of appropriate test materials to conduct such an evaluation. The opinion elaborates on all the above aspects.

### 2. Definitions

**Time-course samples:** refers to samples collected from naturally or experimentally exposed animals, throughout the incubation period from early stages of incubation to clinical onset. These may include some samples from animals known to have been exposed, but which have been culled before clinical onset and where *post-mortem* testing of the CNS is negative.

**Appropriate negative controls:** it is not always possible to access samples from appropriate control animals. Such controls include unexposed animals, and this is particularly important for time-course studies where tests may otherwise be detecting changes arising from ageing or metabolic disturbance. In such circumstances breed, management and sample collection methods systems should be as close as possible to those that apply to the BSE- or scrapie-positive donors. It is also important that where test materials have been stored prior to use, storage conditions (and length of storage) for positive and control animals should be identical, or as close as is practicable, in order to avoid the effects of deterioration while in store.

**Live animal test:** means any test that can be applied to tissue or fluid collected from an animal while still alive, and tested to establish its infection status. This may be at the clinical stage of disease or at any stage of incubation from infection to clinical onset.

### 3. Introduction

In preparation for the new call for an expression of interest for TSE tests to be launched by the EC, the EFSA was requested to update the current protocols for such evaluation, taking into account the experience gained in past evaluation rounds. The first protocol for a field trial for the evaluation of BSE tests for live animals was adopted in July 2004 (EFSA, 2004). That protocol attempted to take into account the state of scientific knowledge and technical experience at that time, but was presented as a first attempt to establish a suitable protocol.

Following the latest call for expression of interest (EC, 2003), one *ante-mortem* test was put forward and accepted for further evaluation, however this test did not pass the full evaluation (EFSA, 2006).

In the meantime, the European epidemic of BSE entered a significant decline. As stipulated in the TSE Road map (EC, 2004), a review of TSE surveillance programmes may now be envisaged. Together, these developments present serious challenges to the further evaluation and approval of live-animal tests. In particular, opportunities to collect reference materials

required for the evaluation of tests are declining. This is particularly important in the early stages of the development of a test, where the availability of high quality tissues/fluids is essential in order to prevent artefacts caused by deterioration of samples after collection or in storage.

This revised protocol is intended to provide guidelines for test developers for the conduct of the preliminary stages of an evaluation process, prior to submission for formal evaluation. It takes into account the experiences gained in evaluating both *post-mortem* and live animal tests, and acknowledges the difficulty of prospectively establishing reference banks to meet the requirements of each test method.

For *post-mortem* testing it is known that the brain as the main target tissue becomes infectious and positive to current rapid test methods in the latter stages of the incubation period (*i.e.* in cattle usually over the age of 30 months). It is recognised that for this reason the testing of the brains of young animals is unlikely to determine whether or not they are infected, and surveillance programmes are therefore planned accordingly.

With respect to live animal testing it is necessary to firmly correlate the changes that a putative test can detect with the infection status and stage of incubation in an individual animal. Negative and positive results are only of value if they can be interpreted with confidence, as the consequences of inaccurate results may be considerable.

Consideration will continue to be given to the establishment of an appropriate bank of samples to enable more extensive evaluation. The fact that archives of materials suitable for conducting the evaluation are finite is acknowledged accordingly. Manufacturers will be obliged to undertake and complete a significant amount of work to establish proof of principle before a formal evaluation can begin. This protocol outlines the criteria that are to be used when considering whether any proposed live animal test for ruminants should be accepted for formal evaluation. The protocol presented here will enable thorough consideration of background supporting data, the constraints imposed by the test matrix chosen, and the availability of appropriate reference materials to enable such an evaluation.

#### **4. Purpose**

Regulation (EC) No 999/2001 lays down the rules of the monitoring programme for TSEs within the European Community based on active and passive surveillance which included a screening procedure using rapid tests. While it might be envisaged that a live animal test could be applied for one or both purposes, proof of the reliability of a live animal test when used for these purposes is more difficult to attain than for *post-mortem* tests. Application of such tests has been anticipated in the EC TSE road map (EC, 2004); however, final decision on the intended usage remains with the EC.

#### **5. Evaluation process**

##### **5.1. General principle**

Evaluation of TSE *post-mortem* tests submitted following a call for an expression of interest launched by the EC follows a series of steps:

1. Assessment of the submitted dossier;
2. Evaluation including
  - a. a pre-evaluation assessment and report;

- b. a laboratory evaluation and report;
  - c. a field trial and report;
3. An evaluation of the report by the EFSA Expert Working Group on TSE testing with final recommendation regarding the approval or otherwise of the submitted and evaluated tests.
  4. Evaluation and approval of the package insert.

Steps 1) and 2a) are carried out by an EFSA Expert Working Group on TSE testing. Steps 2b) and c) covering the laboratory evaluation, the field trial and the respective preparations of the reports are under the responsibility of IRMM<sup>3</sup> which is also responsible for the sample distribution, data collection and analysis, and reporting. The EFSA Expert Working Group on TSE testing is responsible for the evaluation of the reports and evaluation of any package insert developed prior to approval. At any stage, a test may be excluded from further assessment.

Note that for live animal tests evaluation, the protocol as described above stops at the point of assessment of the submission and the evaluation of a preliminary dossier. Again, the EFSA Expert Working Group on TSE testing is responsible for these steps 1 and 2a). At any stage, a test may be excluded from further assessment.

## **5.2. Assessment of submitted dossier**

The manufacturer will be required to provide information addressing all points listed in the call, as part of its submission-dossier along with data to support all claims. In particular the manufacturer is requested to:

1. Specify the target species for which the test is intended.
2. Provide sufficient information on the test to demonstrate that proof of principle has been established, with details of the test method and analyte being measured. Where development is already advanced and supporting evidence in the dossier is robust and verified, consideration may be given to a reduced formal evaluation. Absolute criteria for acceptance in terms of sensitivity and specificity cannot be specified at this stage, but will be considered in the light of data presented and policy needs at the time of submission.
3. Ensure that data presented include results of testing of a panel of un-blinded samples of each tissue type for which a claim is made from at least 10 positive and 30 negative samples<sup>4</sup> from clinically affected animals (*i.e.* suspected of being clinically affected with BSE or scrapie, and tested *post-mortem* with either positive or negative results). Negative control will be from healthy animals<sup>5</sup> or animals found to be suffering from other known neurological diseases. For positive animals, the TSE status of the animals from which samples have been selected should have been confirmed using either an EU approved rapid test or OIE confirmatory method to define the provenance of the particular sample. For negative animals all comprehensive data allowing the establishment of the individual status (test on tissue, geographical origin) should be provided. The manufacturer should further provide details of the origin of all the samples (age and species of animals, type of tissue,

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<sup>3</sup> Institute for Reference Materials and Measurements (IRMM) of the Joint Research Centre (JRC) of DG Research of the European Commission.

<sup>4</sup> Numbers of samples to be tested are based on availability of samples rather than on statistics. Statistically sound numbers of samples to be tested in the full evaluation will be defined.

<sup>5</sup> The Panel recognises that the use of control tissues and fluids from healthy animals is less rigorous than sourcing these materials from TSE-negative animals with other neurological diseases. However, few control samples are currently available from cattle or sheep with other neurological diseases and, in practice, the preliminary evaluation may have to use controls from healthy animals.

age and storage conditions for sample, method used to prepare sample if macerates are used). Samples should be tested as replicates to provide evidence of repeatability.

4. Ensure that results also include the testing of a further test panel comprising a minimum of 30 BSE cattle or 60 scrapie small ruminant positive samples and a minimum of 100 negative controls (as defined above) tested blind. Samples should have been blinded by a third party who may include the institute that supplies the samples. Decoding should be carried out, and results subsequently certified, by that third party. Where the supplying institute has financial interest in the outcome, certification should be provided by a third party, such as a National Reference Laboratory.
5. Include details of all test methods used to test samples and to confirm status, as well as the locations and timing of testing. Evidence that the test method is capable of being transferred from laboratory to laboratory without impact on test performance is required.
6. Provide any additional information, on demand of the EC, on test set-up and performance.
7. In terms of future marketing of the intended test the manufacturer should take account of the following:
  - If the test is to be marketed solely as a test for use on clinically affected animals, in support of national control programmes, further testing on animals in the preclinical stages of infection is not required.
  - Where the company aims to market the test for use on animals in a preclinical stage of incubation, perceived to be healthy, then additional proof of principle is required including test data on time-course samples from a minimum of 20 experimentally (orally) or naturally infected animals, and an equivalent number of comparable age, breed and genotype (for sheep) comprising matched negative control animals. As above, it will be necessary to submit details of the source animals, verified by the institute of origin. Again, the final results must be verified by a third party, which may be the supplying institute providing it has no financial interest in the test.

### **Confidentiality**

All data generated during the above process along with discussions in the EFSA Expert Group on TSE Testing will be treated confidential and not be made accessible to third parties.

### **5.3. Pre-evaluation assessment**

An initial assessment of the reliability of each applicant-manufacturer will be performed before the formal evaluation begins. This evaluation will involve:

1. A visit to the manufacturer's premises (by IRMM<sup>6</sup>), in order:
  - to see the test being performed;
  - to inspect the kit production and quality control facilities;
  - to clarify any issues arising from examination of the submitted dossier
2. During the visit the manufacturer will be required to test a panel of samples supplied by IRMM<sup>7</sup>. This will allow making a preliminary assessment of the method, and comparing performance with the manufacturer's claims.

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<sup>6</sup> In collaboration with CRL.

3. The number of samples involved at this stage will be defined when the evaluation protocol is finalised. The specific nature of all test material provided (positives and negatives) will depend on a preliminary discussion with the company, especially dependent upon the test matrix required and availability of materials.

A report will then be prepared by the EFSA Expert Working Group and TSE testing. The report will include a final decision on tests to be recommended, or otherwise, for full evaluation. This report will be made public.

#### **5.4. Criteria for admission to full evaluation**

At this stage, the use of an ante-mortem test and the species and type of sample required for its preliminary evaluation are not defined and so it is inappropriate to be too specific about the number of negative and positive cases from which samples can be analysed. This will be determined by simple availability from the named resource centres: the VLA or FLI Archives or INRA (see Annex), and any criteria for test sensitivity and specificity will need to be statistically consistent with the numbers and type of sample that can be used in this preliminary evaluation.

Some points related to the eventual use of tests and guidelines on possible criteria for inclusion or exclusion of tests for further evaluation are required to be taken into account:

1. Use of tests and the relative importance of diagnostic specificity and sensitivity

The intended use of diagnostic tests is very important as the key parameter for risk management is the predictive value of a test. The predictive value of a test is a function of the prevalence and its diagnostic sensitivity and specificity.

The predictive value of a positive test is determined by its diagnostic specificity which is the key parameter to define in low prevalence situations such as screening for TSE monitoring and surveillance purposes.

In potential high prevalence situations - such as testing clinical suspects or birth cohorts - the critical parameter is the predictive value of a negative test which is determined by the diagnostic sensitivity. If needed in high prevalence situations, the predictive value of a positive test and hence the diagnostic specificity of the procedure can be improved by adding a confirmative test which may require an assessment *post-mortem*.

2. Guidelines on preliminary selection criteria for further evaluation of a test

Considering the current stage in knowledge and potential scarcity of appropriate biological samples to conduct the pre-evaluation process, no binding performance requirement is felt appropriate at this stage and a recommendation for further evaluation will be at the discretion of an EFSA assessment panel.

However, as a guideline, we would recommend for further evaluation:

- If the intended application is for clinically-affected animals, tests which, when applied to a blinded sample panel, (*i.e.* 30 positive cattle BSE samples, 60 Scrapie positive samples and 100 negative samples) would result in 0-2 failures to detect cattle BSE confirmed positive case, or 0-4 failures to detect scrapie confirmed positive case and 0-2 false positive results.

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<sup>7</sup> In collaboration with the CRL and FLI or INRA.

- If a pre-clinical application is envisaged (series of time course samples from at least 20 experimentally orally or naturally infected animals and negative control animals matched for age, breed and genotype (for sheep)) tests which would result in:
  - 0-1 false positives
  - 0-6 failures to detect a confirmed positive case three months before the onset of clinical signs in cattle or at 50 % of the incubation period in sheep (as defined by standard incubation periods in VRQ/VRQ or ARQ/ARQ sheep).

It is emphasised that suggested parameters remain flexible and results from pre-evaluation process will be interpreted by an expert group in the context of a specific test and intended application.

## **6. Preparation for submission of a test for evaluation**

Companies may find difficulties in accessing samples for test development work, especially where prospective sampling is required. Several EU National Reference Laboratories or Institutes have access to limited stores of materials. The institutes with access to significant numbers of preclinical samples or live animals that can be sampled prospectively are even more limited. Contact details of institutes that may be able to provide materials are listed at Annex 1.

The criteria established for the evaluation of a live animal test are rigorous. They recognise the difficulties of achieving this goal as well as of the cost and complexity of establishing and undertaking a full evaluation. In recognition of the considerable outlay that will be necessary on the part of companies to reach a point at which entry into a formal evaluation is accepted, it can be anticipated that the evaluation protocol may take into account the preliminary work done by minimising the scale of subsequent testing insofar as is possible. Therefore and given the scarcity of test materials it is important that such a pre-evaluation is not seen as an alternative for thorough determination of test potential. Taking into account these issues such as supply of test materials, ease of sampling on farm/abattoirs in live animals, it is anticipated that the following tissues/fluids represent the most appropriate and reliable targets for live animal testing:

1. In cattle: serum, plasma, whole blood, buffy-coat, urine, CSF (the latter may be available but unlikely to be a practical target on farm).
2. In sheep: serum, plasma, whole blood, buffy-coat, urine, biopsies of lymphoid tissue (*i.e.* pharyngeal tonsil, or recto-anal mucosal lymphoid tissue (RAMALT)).

## **CONCLUSIONS**

1. This opinion outlines a general proof of principle and provides preliminary guidance to test developers regarding the necessary investigations that should precede any formal evaluation.
2. Considering the current stage in knowledge and potential scarcity of appropriate biological samples to conduct the pre-evaluation process, no binding performance requirement is felt appropriate at this stage and a recommendation for further evaluation will be at the discretion of an EFSA assessment panel.
3. This protocol needs to be reviewed once the call has been closed and the submissions evaluated. This review will consider the tissues to be used.

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## **APPENDIX**

List and addresses of institutes with access to samples from naturally and experimentally infected animals that may be able to assist in the supply of test materials.

### **Veterinary Laboratories Agency**

Woodham Lane  
Addlestone  
Surrey  
KT15 3NB  
United Kingdom  
<http://www.defra.gov.uk/corporate/vla/science/science-tse-arc-intro.htm>

### **Friedrich-Loeffler-Institut (FLI)**

Federal Research Institute for Animal Health  
Südufer 10  
17493 Greifswald - Insel Riems  
Germany

### **INRA UMR INRA ENVT 1225**

23 chemin des capelles  
31076 Toulouse  
Contactperson: o.andreoletti@envt.fr

### **INRA IASP**

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